REMARKS

Applicants respectfully request reconsideration of the application in light of the arguments presented below.

The 35 U.S.C. § 103 Rejection

Claims 1-4, 6, 8, 10-11, 13-18, 20-22, 24-28, and 30-33 stand rejected under 35 U.S.C. 103 as being obvious over the teachings of the Sorenson reference. Applicants respectfully traverse.

Applicants respectfully contend that the Office has improperly characterized the teachings of the Sorenson reference. For example, the Action states that Sorenson teaches purifying extracellular DNA from blood plasma from a human subject (with cancer and without cancer) to prepare extracted extracellular DNA encoding a mutated gene (K-ras oncogene) (citing page 7, paragraph 2; page 8, paragraphs 1-2, page 12, paragraph 1 and page 25, line 1-6), indicating use of normal DNA sample and tumor DNA sample. However, a review of the only substantive mention of the type of blood plasma sample useful in the assays described in the Sorenson reference is found at page 7, paragraph 2, as follows:

> The detection of mutated DNA, such as specific single copy genes, is potentially useful for diagnostic purposes, and/or for evaluating the extent of a disease. Normal plasma is believed to contain about 10pg of soluble DNA per ml. The concentration of soluble DNA in blood plasma is known to increase markedly in individuals with cancer and some other diseases. The ability to detect the presence of known mutated gene sequences, such as K-ras gene sequences, which are indicative of a medical condition is thus highly desirable. (Emphasis added)

It can be seen that this teaching does not state that mutant DNA can be detected in blood plasma samples from a human without cancer. It merely says that soluble DNA can be detected in small amounts in normal blood plasma samples, and that the amount of this DNA increases in individuals with cancer. Detecting “known” mutated gene sequences, such as K-ras (*i.e.*, known to be associated with cancer), which are indicative of a medical condition (*i.e.*, cancer) is thus highly desirable. Thus, it can be seen that although Sorenson teaches detecting mutated K-ras DNA in blood plasma from cancer patients, the reference does not teach detecting any mutated DNA whatsoever from samples taken from individuals without cancer, as required by Applicants' pending claims. The reference consistently discusses detecting mutated DNA by PCR amplification in “patient samples” (see, for example, page 13, last paragraph; page 23, lines 7-10). In fact, the reference has no actual demonstration that mutated DNA can be detected, even in cancer patients.

The Action asserts that the Sorenson reference "suggests that the detection of mutant gene in normal individuals and presence of said mutant gene could be used as a diagnostic marker for the presence of a cancer, including adenocarcinomas," citing page 2, paragraphs 1-3 of the Sorenson reference. However, Applicants respectfully contend that the cited portion of the reference does not so teach, particularly when considered in combination with the preceding paragraph:

> Soluble DNA is known to exist in the *blood of healthy individuals* at concentrations of about 5 to 10 ng/ml. It is believed that soluble DNA is *present in increased levels in the blood of individuals having* autoimmune diseases, particularly systemic lupus erythematosus (SLE) and other *diseases including* viral hepatitis, *cancer* and pulmonary embolism. *It is not known* whether circulating soluble DNA represents a *specific type of DNA* which is particularly prone to appear in the blood. However, studies indicate that the DNA behaves as double-stranded DNA or as a mixture of double-stranded and single-stranded DNA, and that it is likely to be composed of native DNA with single-stranded regions. Dennin, R. H. (1979) Klin. Wochenschr. 57:451-456. Steinman, C. R. (1984) J. Clin. Invest. 73:832-841. Fournie, G. J. et al. (1986) Analytical Biochem. 158:250-256. There is also evidence that in patients with SLE, the circulating DNA is enriched for human repetitive sequence (Alu) containing fragments when compared to normal human genomic DNA.
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> *In patients with cancer*, the levels of circulating soluble DNA in blood are significantly increased. Types of cancers which appear to have a high incidence of elevated DNA levels include pancreatic carcinoma, breast carcinoma, colorectal carcinoma and pulmonary carcinoma. *In these forms of cancer*, the levels of circulating soluble DNA in blood are usually over 50 ng/ml, and generally the mean values are more than 150 ng/ml. Leon et al. (1977) Can. Res. 37:646-650; Shapiro et al. (1983) Cancer 51:2116-2120.
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> *Mutated oncogenes have been described in experimental and human tumors*. In some instances certain mutated oncogenes are associated with particular types of *tumors*. Examples of these are adenocarcinomas of the pancreas, colon and lung which have approximately a 75%, 50%, and 35% incidence respectively, of Kirsten ras (K-ras) genes with mutations in positions 1 or 2 of codons 12. The most frequent mutations are changes from glycine to valine (GGT to GTT), glycine to cysteine (GGT to TGT), and glycine to aspartic acid (GGT to GAT). Other, but less common mutations of codon 12 include mutations to AGT and CGT. K-ras genes in somatic cells of such patients are not mutated.
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> The ability to detect sequences of mutated oncogenes or other genes in small samples of biological fluid, such as blood plasma, would provide a useful diagnostic tool. *The presence of mutated K-ras gene sequences in the plasma*

> *would be indicative of the presence in the patient of a* ***tumor*** *which contains mutated oncogenes*. Presumably this would be a *specific tumor marker* since there is *no other known source of mutated K-ras genes*. Therefore, this evaluation may be useful in suggesting and/or confirming a diagnosis. The amount of mutated K-ras sequences in the plasma may relate to the size of the tumor, the growth rate of the tumor and/or the regression of the tumor. Therefore, serial quantitation of mutated K-ras sequences may be useful in determining changes in *tumor mass*. Since most human cancers have mutated oncogenes, evaluation of plasma DNA for mutated sequences may have very wide applicability and usefulness. (*Emphasis added*.)

Applicants respectfully contend that there is nothing in the cited passage concerning detecting mutated DNA in an individual without cancer, an explicitly-recited limitation of their pending claims. Applicants respectfully contend that the Action thus mischaracterizes the teachings of the Sorenson reference, and that the passages cited in support of the obviousness rejections in the Action do not support those rejections. There is no teaching (nor suggestion or motivation) of detecting mutated DNA from an individual without cancer in the cited passages or anywhere else in the reference.

Applicants respectfully contend that the Office has impermissibly used hindsight to reconstruct their invention from Sorenson's teachings. The existence of soluble DNA in blood plasma or serum does not render obvious detection of mutated DNA of any kind, even in individuals with cancer. The mere fact that the amount of soluble DNA increases in cancer patients may suggest that, *for cancer patients*, DNA associated with their cancer (like mutated K-ras) could be detected. There is no support in the Sorenson reference for Applicants' invention that mutated DNA can be detected in blood plasma from individuals without cancer. The cited art being devoid of any teaching of Applicants' invention, Applicants respectfully contend that the skilled worker would have had no reasonable expectation of success in detecting mutated DNA in individuals without cancer.

In view of the limitations in the teachings of the Sorenson reference, Applicants respectfully contend that the Office has not made out a *prima facie* case of obviousness against their pending claims, and requests that these grounds of rejection be withdrawn.

The Sorenson reference is also asserted in combination with the Ronai reference in support of a rejection under 35 U.S.C. §103 of claims 5 and 9. The deficiencies of the Sorenson reference are set forth above and apply with equal vigor to this ground of rejection. The teachings of the Ronai reference do not overcome these deficiencies, since the Office acknowledges that this reference merely teaches the use of restriction enzyme digestion to enrich a human genomic DNA sample for a mutant DNA sequence, specifically mutant K-ras DNA., However, this reference is silent towards embodiments for detecting amplified DNA from human blood plasma, and indeed teaches using intracellular DNA (*i.e.*, genomic DNA isolated from cells). The reference being silent as to detecting DNA from blood plasma or serum (*i.e.*, extracellular DNA), the combination of the Sorenson and Ronai references do not render obvious the instantly-claimed invention.

Claims 7 and 19 are rejected under 35 U.S.C. §103 as being obvious over the combination of the Sorenson reference and the Breivik reference. The deficiencies of the Sorenson reference are set forth above and apply with equal vigor to this ground of rejection. The teachings of the Breivik reference do not overcome these deficiencies, since the Office acknowledges that this reference merely teaches the use of a solid support to isolate amplified DNA fragments, including magnetic particles as solid support. The Breivik reference is silent towards embodiments for detecting amplified DNA from human blood plasma. The reference being silent as to detecting DNA from blood plasma or serum (*i.e.*, extracellular DNA), the combination of the Sorenson and Breivik references do not render obvious the instantly-claimed invention.

Claim 29 is rejected under 35 U.S.C. §103 as being obvious over the combination of the Sorenson reference and the Moran reference. The deficiencies of the Sorenson reference are set forth above and apply with equal vigor to this ground of rejection. The teachings of the Moran reference do not overcome these deficiencies, since the Office acknowledges that this reference merely teaches the use of sigmoidoscopy. The Moran reference is silent towards embodiments for detecting amplified DNA from human blood plasma. The reference being silent as to detecting DNA from blood plasma or serum, the combination of the Sorenson and Moran references does not render obvious the instantly-claimed invention.

Claims 12 and 23 are rejected under 35 U.S.C. §103 as being obvious over the combination of the Sorenson reference and the Albertson reference. The deficiencies of the Sorenson reference are set forth above and apply with equal vigor to this ground of rejection. The teachings of the Albertson reference do not overcome these deficiencies, since the Office acknowledges that this reference merely teaches detecting mutations in the APC gene. The Albertson reference is silent towards embodiments for detecting amplified DNA from human blood plasma. The reference being silent as to detecting DNA from blood plasma or serum, the combination of the Sorenson and Albertson references do not render obvious the instantly-claimed invention.

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CONCLUSION

Applicants respectfully submit that all requirements of patentability are fully met, and allowance of the claims is respectfully requested.

If the Examiner believes it to be helpful, she is invited to contact the undersigned attorney by telephone at 312-913-0001.

Respectfully submitted,
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